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【 CASE REPORT 】

Pemetrexed-induced Interstitial Lung Disease Mimicking Hypersensitivity Pneumonia: A Pathologically Proven Case

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Abstract:
We herein report a 45-year-old woman with lung adenocarcinoma stage IV (cT4N3M1a). She was treated with pemetrexed (PEM) monotherapy following four cycles of first-line treatment with carboplatin, paclitaxel, and veliparib. After three cycles of PEM treatment, she presented with dyspnea, and chest computed tomography showed diffuse ground-glass attenuation (GGA), suggesting hypersensitivity pneumonia (HP). Bronchoalveolar lavage revealed a marked increase in lymphocytes (90.5%), and a transbronchial lung biopsy confirmed lymphocytic alveolitis with granuloma. Because her symptoms and diffuse GGA were spontaneously resolved with PEM discontinuation alone, PEM-induced interstitial lung disease was diagnosed. Chest physicians should be aware that PEM can induce HP-type interstitial lung disease.

Key words: pemetrexed, hypersensitivity pneumonia, methotrexate

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Introduction

Pemetrexed (PEM) is an anti-folate drug that exerts an antitumor effect by inhibiting folate metabolism (1). Interstitial lung disease (ILD) is a fatal adverse event caused by chemotherapeutic agents, and PEM occasionally causes ILD with a reported incidence of 1.8% according to a post-marketing surveillance study (2).

While PEM-related ILD is generally reported to show diffuse ground-glass opacity with a non-specific interstitial pneumonia (NSIP) pattern or organizing pneumonia (OP) pattern, most patients are not pathologically but rather radiologically diagnosed (3, 4). We herein report a pathologically proven case of PEM-induced ILD mimicking hypersensitivity pneumonia (HP).

Case Report

A 45-year-old woman with a smoking history (1 pack/day for 25 years) and no occupation visited our hospital with a complaint of chronic cough for the past 3 months. Contrast-enhanced computed tomography (CT) revealed a 28×25 mm nodule in the upper lobe of the right lung and pericardial thickening with mediastinal and hilar lymphadenopathy. She was diagnosed with stage IV (T4, N3, M1a) (UICC ver.7) lung adenocarcinoma in October 2015 (Fig. 1). A molecular analysis showed neither epidermal growth factor receptor (EGFR) mutations nor anaplastic lymphoma kinase (ALK) rearrangements.

She was enrolled in a clinical trial (Veliparib trial) and treated with carboplatin, paclitaxel, and veliparib, which is a potent oral inhibitor of poly-ADP-ribose polymerase (PARP), as the first line chemotherapy regimen in October 2015. After 4 cycles of this regimen, the disease became stable, and she was treated with PEM monotherapy in combination with daily folic acid supplement based on the protocol. Although her lung cancer remained stable after three cycles of PEM, she developed a low-grade fever at the end of April 2016, and dyspnea gradually appeared in early May

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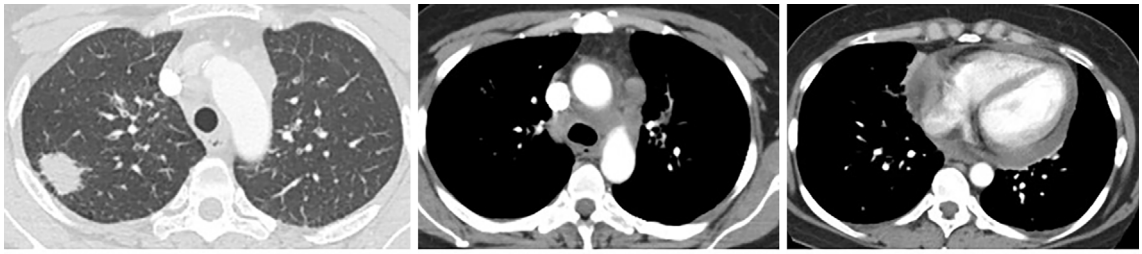

Figure 1. **Chest high-resolution computed tomography showed a nodule in the right upper lung at the initial visit (A). Contralateral mediastinal lymphadenopathy and pericardial effusion were also observed (B, C).**

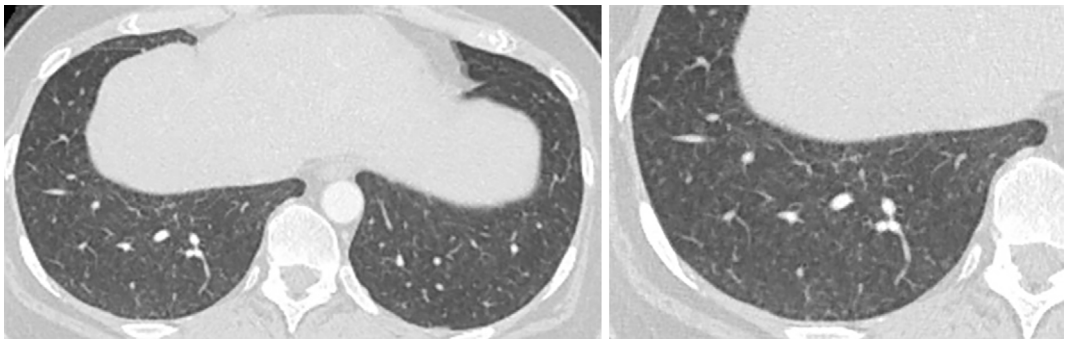

Figure 2. **Chest high-resolution computed tomography showed diffuse ground-glass attenuation with centrilobular nodules.**

Table. **Laboratory Data.**

Hematology		Arterial blood gas analysis (Room air)	
WBC	4,980 /μL	pH	7.43
Neu	56.5 %	PaO_2	89.0 Tor
Lym	18.3 %	$PaCO_2$	37.5 Tor
Eos	10.5 %		
Hb	9.9 g/dL		
Plt	45.0 ×10⁴/μL		
Biochemistry		**Bronchoalveolar lavage**	
Cr	0.55 mg/dL	Cell count	5.2 ×10⁵/mL
BUN	14.5 mg/dL	Mac	8.0 %
AST	42 IU/L	Lym	90.5 %
ALT	34 IU/L	Neu	0.0 %
LDH	306 IU/L	Eos	1.5 %
CRP	0.26 mg/dL	CD4/8	2.1
KL-6	1,004 U/mL		
CEA	510 ng/mL		

KL-6: Krebs von den Lungen-6, CEA: carcinoembryonic antigen

2016. On admission, her saturation was 95% under room air conditions and a physical examination did not reveal any crackles on chest auscultation. Although chest radiograph showed no abnormal findings, chest high-resolution CT showed diffuse ground-glass attenuation (GGA) and centrilobular nodules with lower lobe predominance, which was suggestive of HP or PEM-induced ILD (Fig. 2). According to a medical interview, she had no history of inhalation, such as mold in her home, close exposure to birds or humidifier use. Because ILD developed three months after the final administration of carboplatin, paclitaxel and veliparib and no drugs had been newly added, ILD caused by a drug other than PEM was denied.

Laboratory examinations revealed the elevation of serum Krebs von den Lungen (KL)-6 (from 593 U/mL to 1,004 U/mL) and serum lactate dehydrogenase (LDH) (from 216 IU/L to 306 IU/L) (Table). Bronchoalveolar lavage fluid (BALF) obtained from the left middle lobe (B5a) showed a total cell count of 5.2×10^5 cells/mL and increased lymphocytes up to 90.5% with a CD4/CD8 ratio of 2.1 and normal cytology. The bacterial culture of the BALF was negative. A transbronchial lung biopsy (TBLB) specimen from the left lower lung (Segment 8) showed fibrotic thickening of the alveolar septum and alveolitis with granuloma (Fig. 3). The patient was carefully observed without steroid therapy but with continuing daily folic acid supplement. However, the symptoms and radiological findings apparently improved simply by discontinuing PEM in mid-June 2016 (Fig. 4). Based on these results, PEM-related ILD was diagnosed.

A serological examination performed after the diagnosis of PEM-related ILD showed that the levels of LDH had gradually decreased to 231 IU/L at the time of the disappearance of GGA. In contrast, the levels of serum KL-6 paradoxically continued to increase to 1,550 U/mL in accordance with the increase of carcinoembryonic antigen (CEA) from 510 to 1,968 ng/mL in mid-June 2016, indicating that

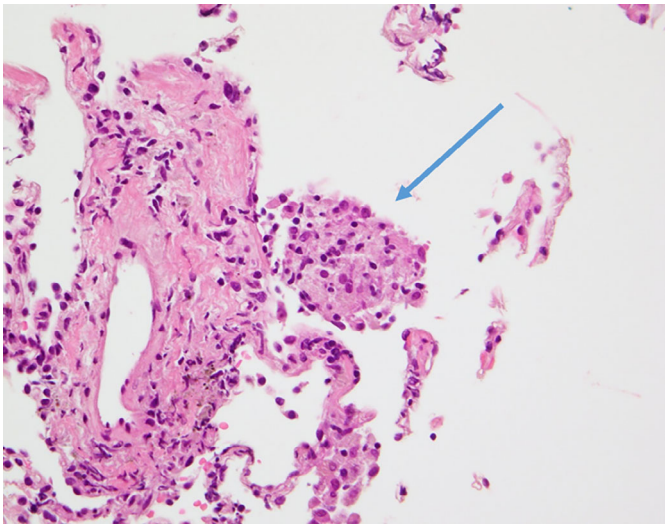

Figure 3. **A transbronchial lung biopsy revealed pulmonary alveolitis with lymphocyte infiltration and granuloma (arrow).**

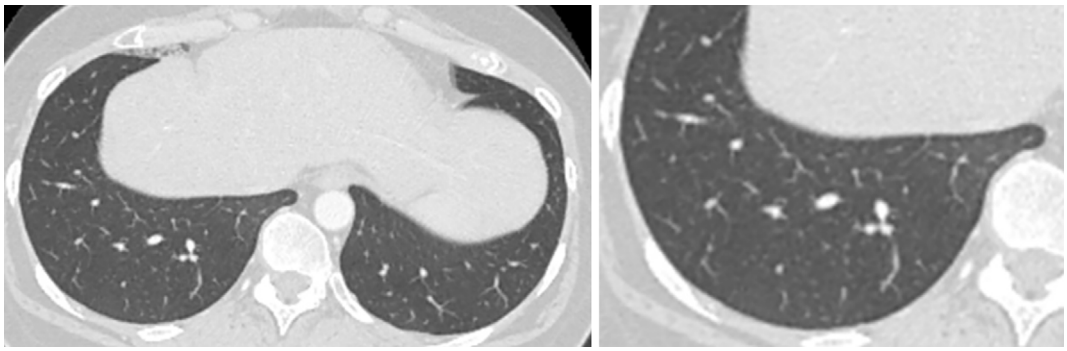

Figure 4. **Ground-glass attenuation was apparently improved with only the discontinuation of PEM.**

the paradoxical increase in KL-6 had been caused by tumor progression following PEM withdrawal.

Although the patient survived for 1.8 years thereafter and was treated with subsequent chemotherapeutic agents, including nivolumab, docetaxel, S-1 and vinorelbine, her ILD never relapsed. This clinical course also confirmed the diagnosis as PEM-related IP, not HP.

Discussion

We herein report a case of HP-type PEM-induced ILD. In a post-marketing surveillance study on PEM-related ILD in Japan (2), PEM-related ILD reportedly developed in 12 of 683 non-small cell lung carcinoma (NSCLC) patients (1.8%), and 8 of these 12 patients developed diffuse GGA. However, whether or not these patients had HP-type ILD, as in our case, is unclear. The present findings suggest two clinical implications. First, PEM can cause HP-type ILD. In fact, ILD in our patient was pathologically and radiologically consistent with HP-type ILD based on the presence of alveolitis with granuloma and radiological diffuse GGA and centrilobular nodules. Of note, HP was able to be clinically excluded based on the patient's clinical course, wherein ILD spontaneously regressed with PEM discontinuation alone and never relapsed thereafter. To our knowledge, there have only been three cases of pathologically evaluated PEM-related ILD; the ILD patterns in those cases were diffuse alveolar damage, NSIP and OP (one each) (3-5). We therefore believe that this is the first report of HP-type ILD caused by PEM.

Second, PEM-related ILD can be induced by a hypersensitivity mechanism. It remains unclear whether PEM-related ILD is caused by hypersensitivity or some other mechanism, such as toxic a reaction due to the accumulation of the drug within the lung tissue. Several studies have described a poor correlation between the clinical onset of pneumonitis and the duration of PEM therapy, suggesting that PEM-related ILD is caused by a hypersensitivity mechanism, not a toxic reaction (5). We believe that the existence of methotrexate (MTX)-related ILDs supports this supposition. MTX is an anti-folate drug, like PEM, and is well known to cause ILD, with a prevalence of 0.3-7.5%. Of note, MTX-induced ILD often presents as HP-type ILD (6, 7). In MTX-induced ILD, the CD4/8 ratio in BALF reportedly depends on the time since the onset of pneumonitis, but it is increased in the acute phase (8). In addition, alveolar lymphocytosis, granu-

loma formation and a poor correlation of the onset of MTX-related ILD and the duration of MTX therapy have been reported, indicating that HP-type MTX-induced ILD is caused by a hypersensitivity mechanism (7-10). Although the CD4/8 ratio was not markedly increased in the present case, and there are few reports describing the CD4/CD8 ratios in BALF of PEM-related ILD, the present case shares many characteristics in common with those of patients with MTX-related ILD. Given that both MTX and PEM are anti-folate drugs, HP-type PEM-related ILD may indeed be caused by a hypersensitivity mechanism.

In conclusion, we encountered a case of pathologically proven PEM-related HP-type ILD. Chest physicians should be aware that HP-type ILD can develop, albeit rarely, in NSCLC patients treated with PEM. The accumulation of case series will confirm our results.

The authors state that they have no Conflict of Interest (COI).

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